REMARKS/ARGUMENTS

The Status of the Claims.

Claims 1 to 3, 6, 8 to 10, 12, 15 to 19, 21 and 22 are pending with entry of this amendment, claims 4, 5, 7, 11, 13, 14, 20 and 23 to 65 being cancelled. Claims 1, 9, 10, 12 and 15 are amended herein. These amendments introduce no new matter and support is replete throughout the specification. These amendments are made without prejudice and are not to be construed as abandonment of the previously claimed subject matter or agreement with any objection or rejection of record.

With respect to amended claim 1, support for the specific O-RSs and O-tRNAs can be found throughout the specification. Applicants note that amendments include aspects incorporated from currently cancelled claims 7 and 11. Further support can be found, e.g., at paragraphs 26, 129, 192 and 194.

With regard to claims 9, 10 and 15, the amendments merely delete an objected term.

With regard to claim 12, the amendment merely corrects dependency in light of cancelled claim 11.

Applicants submit that no new matter has been added to the application by way of the above Amendment. Accordingly, entry of the Amendment is respectfully requested.

35 U.S.C. §112, First Paragraph.

Claims 1 to 3, 6, 8 to 13, 15 to 19, 21 and 22 were rejected under 35 U.S.C. §112, first paragraph, for allegedly inadequate written description. To the extent the rejection is deemed applicable to the amended claims, Applicants traverse.

The written description requirement may be satisfied if claim terms "readily convey distinguishing information concerning their identity, such that one of ordinary skill in the art could visualize or recognize the identity of a member of the genus." See, *Amgen Inc. v. Hoescht Marion Roussel, Inc.* 65 USPQ2d 1385 (Fed. Cir. 2003). According to MPEP 2163, the description need only describe in detail that which is new or not conventional. The

written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. See also, *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406. Here, currently amended claims are fully supported with descriptions of multiple practiced structures and identification of key characteristics and structures described in the specification as correlated with function.

The rejections of the prior claims were based on the allegation that the "claims encompass an undefined genus of lysyl-O-tRNA and/or lysyl-O-RS molecules that only fit a desired functional characteristic." However, the currently amended claims include, e.g., particularly described O-RSs and O-tRNAs defined by identified functional structures.

Although the claims are still limited by the requirement that the structures have a minimal functional efficiency compared to a given standard, the currently amended claims now require the O-tRNA and the O-RS to have structures identified in the original specification as providing the desired function. For example, the O-RS can be a given O-RS (having a specific extensive truncation over wild type identified as eliminating toxicity in *E. coli*) or an I41 and S268 mutant thereof (identified as the most active structure of 5 different functioning O-RS clones in hGln charging) with at least 95% identity to SEQ ID NO 28. AND, the O-tRNA must have the identified robust suppressor anticodon loop, plus at least 95% identity to the functional structurally described consensus sequence SEQ ID NO 26.

The independent claim has been further amended to delete the objected "modified variant thereof" term. The standard reference translation system is further clarified as including both the I41 and (not "and/or") S268 in the RS.

Support for translation systems comprising the specific functional O-RS and O-tRNA can be found throughout the specification. In particular, see the identified anticodon loop structure in paragraph 194; functional structure descriptions and variants of O-tRNAs in Example 1, starting at paragraph 192, and in Figure 5; functional structure descriptions and variants of O-RSs in Examples 2 and 3, starting at paragraph 201; and

multiple functional combinations of the claim elements described at paragraph 121. Applicants have had in their possession, and described, the separate components of the claimed translation systems, and the combination of system components.

The separate translation system components have been amended to require close identification with components provided in the original specification, including mandatory identified function-correlated structures. The well described claim 1 translation system components are now together in the described and functional combination, instead of in separate (now cancelled) dependent claims. Because the claims are now directed to well characterized components and component combinations, and limited to functional structures described in the original specification, Applicants respectfully request withdrawal of the rejections for alleged lack of adequate written description.

Claims 1 to 3, 6, 8 to 11, 15 to 19, 21 and 22 were rejected under 35 U.S.C. §112, first paragraph, for alleged lack of enablement. To the extent the rejection is deemed applicable to the amended claims, Applicants traverse.

To be an enabling disclosure under § 112, first paragraph, a patent must contain a description that enables one skilled in the art to make and use the claimed invention. That some experimentation is necessary does not constitute a lack of enablement; the amount of experimentation, however, must not be unduly extensive. *See In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). Whether undue experimentation is required by one skilled in the art is typically determined by reference to eight factors considered relevant to the inquiry: (1) quantity of experimentation necessary; (2) amount of guidance presented; (3) presence of working examples; (4) nature of the invention; (5) state of the prior art; (6) relative skill of those in the art; (7) predictability of the art; and (8) breadth of the claims. *See id.*

The Office has objected that the previous claims were allegedly not enabled for a translation system "comprising any lysyl-ORS/OtRNA ... used to suppress a selector codon by preferentially charging a homoglutamine .." Current claims address this issue by requiring O-RS/O-tRNA pairs with specific structures functioning to charge hGln.

As a preliminary matter, Applicants note that claims 12 and 13 are not rejected for lack of enablement. Of course, in the context of the currently amended claim 1, the thoroughly described claim 12 CUCUAAA or CUUCCUAA sequences must now be considered allowable as both adequately described and enabled. The essential enabled aspect of claim 13, wherein the lysyl-OtRNA comprises SEQ ID NO: 26, has essentially been incorporated into the current claim 1, in combination with additional enabling limitations. Therefore, Applicants expect there is little or no rational remaining for not considering all claims enabled, as discussed below.

The current independent claim 1 is as follows:

> **1.** A translation system comprising:
> an orthogonal lysyl tRNA (lysyl O-tRNA);
> an orthogonal aminoacyl tRNA synthetase (O-RS) that preferentially charges the orthogonal lysyl tRNA with homoglutamine; or
> the orthogonal lysyl tRNA (lysyl O-tRNA) and the orthogonal aminoacyl tRNA synthetase (O-RS);
> wherein the O-RS is PhΔAD (SEQ ID NO:28), or an I41 and S268 mutant comprising 95% identity to PhΔAD (SEQ ID NO:28);
> and wherein the lysyl O-tRNA comprises an anti-codon loop comprising a CU(X)nXXXAA sequence and at least 95% identity to SEQ ID NO:26:
> wherein the O-RS in combination with the O-tRNA and homoglutamine is at least 50% as effective at suppressing a selector codon as an I41 and S268 mutant of PhΔAD (SEQ ID NO:28; a mutant of *Pyrococcus horikoshii* tRNA synthetase), in combination with an O-tRNA of SEQ ID NO:26 and homoglutamine.

The claim is a close approximation of what has been exemplified in the original specification. The O-RS and O-tRNA are required to be given sequences, or highly identical versions retaining key identified functioning structures. The combinations of translation system elements are limited to only those at least half as functional as a provided standard reference system. Given the guidance provided in this skilled art, one of skill should be enabled to practice the focused scope of the claimed invention without undue experimentation.

Again Applicants note that *In re Wands*, reversed the PTO's determination that claims directed to methods for detection of hepatitis B surface antigens did not satisfy the enablement requirement. The *Wands* Court held that the specification was enabling with respect to the claims at issue and found that "there was considerable direction and guidance"

in the specification; there was "a high level of skill in the art at the time the application was filed;" and "all of the methods needed to practice the invention were well known." 858 F.2d at 740, 8 USPQ2d at 1406. After considering all the factors related to the enablement issue, the Court concluded that "it would not require undue experimentation to obtain antibodies needed to practice the claimed invention." *Id.*, 8 USPQ2d at 1407. Here, as in *Wands* (and discussed above), the level of skill in the art is high and considerable guidance is provided to practice the claimed invention. Further, here the scope of the claims is less broad, the rate of experimental of success is higher, and more working examples and functional structures are provided, than in *Wands*.

Breadth of Claims. The claims are not excessively broad. For example, the presently amended independent claim 1 now includes further functional combinations of limitations from cancelled dependent claims 7 and 11, and further focuses on a readily practicable 95% identity limitations for translation system components. The claimed translation systems are further limited by the requirement that they have a translation efficiency at least 50% of a known standard system. Each of these limitations are extensively described and enabled, as discussed below.

Skill is High. The level of skill is high. The level of skill of practitioners in the field was considered "high" for the *Wands* decision. Obviously, the level of skill in manipulation of biologic systems is much higher now than it was for Wands in 1988. The information that biotechnology practitioners are presumed to be aware of has had over 20 years to develop, and the pace of development during that period has been staggering. A typical postdoctoral researcher or principal investigator can, for example, sequence and provide a detailed analysis of an entire genome, or, e.g., hundreds of cloned RS or OtRNA, in a matter of weeks, whereas in 1988, a week could go by to get one simple sequencing reaction to work, due to the extensive manual manipulations that had to be performed at the time. If the level of skill in the art was "high" at the time of Wands then it is now positively stratospheric. In any case, any moderately competent molecular biologist, given Applicants' disclosure can certainly perform each and every step required to make the claimed systems of, e.g., specific lysyl tRNA/RS pairs to charge homoglutamine at a level, e.g., lower than practiced in the present specification.

Predictability in Preparing Desired Embodiments of the Claimed Systems has been Shown to be Good. The predictability of success is well demonstrated by the pioneering work of the present inventors, who had a high degree of routine success without the hindsight guidance of the present specification. For example, at paragraph 101, the inventors ventured to pair a *Pyrococcus horikoshii* tRNA synthetase with a theoretical consensus tRNA construct, and it functioned as predicted. At paragraph 196, a "halobacterial tRNA was ... anticipated to be readily charged by PhKRS", and it was. At paragraph 209, the theoretical PhΔAD/AK_{CUA} pair was constructed and it functioned as predicted to suppress an amber mutation in an orthogonal system. At paragraph 212, when investigators attempted to mutate an RS to charge its cognate orthogonal tRNA the with the desired homoglutamine unnatural amino acid, 5 of 15 colonies (33%) screened provided different synthetases each functioning in the orthogonal system to incorporate homoglutamine. Applicants note that in the enabled *Wands* claims to screening antibodies, a success rate of only 2.8% was deemed predictable and enabled.

Predictability is further enhanced in current claims by the additional requirement that the O-RS and O-tRNA retain specific structures taught as correlated to the desired function of the claimed system. Further, one of skill would know many of the variants, staying within the required 95% identity, that should likely be avoided to retain, e.g., at least half functionality, or that can likely be conservatively modified, as discussed in the specification. One of skill knows how to make functional substitutions in less critical areas to retain the secondary and tertiary structures that retain the conformation of active sites. For example, because the general alpha helix, beta sheet, turns structure of the *Ph*RS (from which the present RS is derived) was known, one of skill can readily provide a high percentage of active hGln charging variants by conservative substitution, e.g., with amino acids known to retain the known structures. For example, methionine, alanine, leucine, uncharged glutamate, and lysine ("MALEK") have long been known retain alpha helix structures. Regarding beta sheet structures found in active proteins, large aromatic residues (Tyr, Phe and Trp) and β-branched amino acids (Thr, Val, Ile) are favored to be found in β strands in the middle of β sheets. Most such intelligent substitutions, even multiple substitutions, would retain some or all activity. It would not be undue experimentation in the

art to discard the few failures (or even a worse case, a majority of failures) to identify additional functioning RSs based on the given functional RS retaining the key given structures. Failure would be predictably low, and well below the controlling standard set in *Wands*. Teachings are not required to provide even high levels of success. Yet, here it would be predictable that many or most embodiments engineered with skill based on the teachings and limited to the structures of the claims would adequately function.

The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). From the discussion above, it is clear the amount of guidance required to enable the claims should be minimal, however, as discussed below, the guidance provided in the present exceptional specification is exhaustive.

Guidance is Extensive. The "amount of guidance or direction" refers to that information in the application, as originally filed, that teaches how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly stated in the specification. See, e.g., *Chiron Corp. v. Genentech Inc.*, 363 F.3d 1247, 1254, 70 USPQ2d 1321, 1326 (Fed. Cir. 2004). Here, the technology required to practice the invention is reasonably predictable in the hands of one of skill in the well-developed art. Required experimentation is drastically reduced by the comprehensive guidance provided in the specification.

Applicants believe the specification actually teaches one of skill how to reasonably practice embodiments of systems beyond the claimed scope without undue experimentation. The specification describes generically how one of skill can practice the invention to acquire any desired translation system embodiment, within the general scope of the claims, to incorporate homoglutamine into a peptide. The functionality can be improved by directed engineering and/or random mutation and screening of RS and/or tRNA orthogonal components. Finally, the orthogonal RS can be further engineered and/or screened to selectively charge the cognate tRNA with homoglutamine, e.g., based on commonly available RS crystallography data for the RS or related RSs. The original

specification teaches a variety of methods of preparing the claimed system components and combinations, e.g., in the section entitled "Orthogonal tRNA (O-tRNA)" at paragraphs 68 to 84; the section entitled "Orthogonal aminoacyl-tRNA synthetase (O-RS)" at paragraphs 85 to 92; and, the section entitled "Orthogonal Components for Incorporating Homoglutamine" at paragraphs 120 to 136.

Moreover, the specification specifically teaches functional variant species of the claimed systems. For example, structures are described influencing function for the claimed translation system components and component combinations. This guidance greatly enhances the likelihood of success in designing systems of the claims and minimizes experimentation. For example, important structural/functional guidance providing O-tRNAs of the claims includes: the tremendous general knowledge in the art concerning the functions of the "cloverleaf" stem and leaf loop structures of tRNAs; the robust orthogonal suppressor (CU(X)XXXAA) tRNA anticodon loop described in paragraph 194; the consensus and variant suppressor strategies discussed in paragraphs 194 et seq.; inspection of proposed sequences for non-canonical base pairs or base mismatches in stem regions in paragraph 198; and, the identification of a key orthogonal discriminator base 73 discussed at paragraph 195. Specific structural/functional guidance is provided with regard to O-RSs of the claims, substantially reducing required experimentation. For example, in Figure 6 and at paragraphs 121 and 212, key active site amino acid residues E41 and Y268 of PhYRS are identified. Analogous residues would be found generically in other archaeal lysine tRNA synthetases. At paragraph 203, truncation after residue S357 is identified as providing better functionality with tRNAs having anticodon mutations.

Working Examples are Abundant. Working examples are provided for methods to provide functioning system components and to combine and enhance desired components to work together in charging homoglutamine. Further, the original specification provides a number of functioning systems, a range of specific working components, and a number of components that could be modified (using the described methods) to provide functioning component combinations, depending on the desires of the technician.

The body of the specification provides working examples of methods to prepare a broad range of working systems of the invention. The Examples section teaches a

range of specific embodiments of working method process intermediates, working system components and working system combinations.

System components were readily prepared. As noted above, an archaeal tRNA and RS from another Archaeal genus were selected as a functioning pair at paragraph 196. At paragraph 198 an orthogonal archaeal amber suppressor tRNA was constructed that functioned with PhKRS and PhΔRS. The orthogonal archaeal amber suppressor tRNA ultimately functioned to receive homoglutamine. At paragraph 208 PhΔAD was found to preferentially charges whole halobacterial tRNA. PhΔAD was found to function well in combination with tRNAs suppressing either frame shift or amber mutations, see, e.g., paragraphs 240 and 209. At paragraph 211 multiple orthogonal tRNAs were readily cloned that function with PhΔAD. At paragraph 212, five different RS clones were identified in one experiment, working with a lysyl O-tRNA to incorporate homoglutamine.

The working examples demonstrate that functioning orthogonal pairs are readily provided in light of the teachings and references described in the original specification. The working examples include at least five examples of, e.g., claim 1 translation systems. The working examples of methods and intermediate system components enable ready preparation of additional working examples, as desired, without undue experimentation.

Quantity of Experimentation is Minimal to Practice the Claimed Invention. As noted above, because the claims are focused on working examples, the skill in the art is high, guidance is extensive, and success predictable, experimentation would be minimal to practice the invention, as claimed. For example, identification of orthogonal pairs is routine, and it would be easy to provide functional species across the scope of the claims, e.g., while retaining the required functional structures of the claims. The success rate was high in modification of a given orthogonal pair to specifically charge with homoglutamine. The success rate is would be even greater for future practitioners of the invention, given the lessons provided in the original specification. Given the knowledge provided, it should not be considered undue experimentation to provide a system with at least half the efficiency of a given working embodiment standard system.

CONCLUSION

In view of the foregoing, Applicants believes all claims now pending in this application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the claims are deemed not to be in condition for allowance after consideration of this Response, a telephone interview with the Examiner is hereby requested. Please telephone the undersigned at (510) 769-3510 to schedule an interview.

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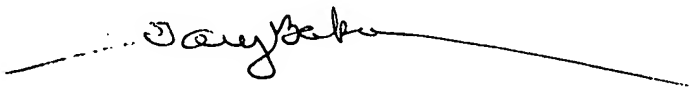
Respectfully submitted,



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Attachments:

1) A transmittal sheet; and,
2) A receipt indication postcard.